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Fas (APO-1/CD95) Ligand and Fas Expression in Renal Cell Carcinomas

Correlation With the Prognostic Factors

Young-Sik Kim, MD,[a] Kwang Hee Kim, MD,[a] Jung-Ah Choi, MD,[a] Ju Han Lee, MD,[a] Han Kycom Kim, MD,[a] Nam Hee Won, MD,[a] and Insun Kim, MD[a]

[a]*From the Departments of Pathology (Drs Y.-S. Kim, J. H. Lee, H. K. Kim, N. H. Won, and I. Kim), Internal Medicine (Dr K. H. Kim), and Diagnostic Radiology (Dr J.-A. Choi), College of Medicine, Korea University, Gojan-Dong, Ansan, Korea.*

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● *Background and Objective.*—Fas ligand (FasL, CD95L) is a type II transmembrane protein of the tumor necrosis factor family that induces cells to send an apoptotic signal to cells expressing Fas (CD95, APO-1). It has been shown that cancers have a dysregulated expression of Fas and FasL system, conferring a survival advantage. It is important to understand FasL and Fas expression in tumors, because the growth of cancer might be controlled by Fas-mediated apoptosis.

Methods.—The expressions of FasL and Fas were studied by immunohistochemical analyses in 51 cases of renal cell carcinomas and the adjacent normal renal tissues, respectively. In addition, their expressions were compared with prognostic factors, such as tumor size, nuclear grade, TNM stage, and histologic types.

Results.—In nonneoplastic renal tissues, FasL was expressed in all

nephron segments, whereas Fas also expressed in all tubules, except for glomeruli. In renal cell carcinomas, FasL protein was detected in 50 (98.0%) of 51 cases, whereas Fas expressed in 38 (74.5%) of 51 cases. In fact, the immunostaining of Fas was less intense than that in the adjacent normal segments of all cases. The staining pattern showing both high expression of FasL and low expression of Fas was found in 36 (70.6%) (P = .04) of 51 cases, most of which were Fuhrman grade 2 or 3 tumors. However, the expression pattern did not correlate statistically with the tumor size, histologic type, or clinical stage. On the other hand, most grade 4 tumors displayed high expression of both FasL and Fas (P < .001).

***Conclusion.*—These data indicate that high expression of FasL and low expression of Fas protein in renal cell carcinomas may play a role in evading surveillance of the immune system. In addition, the FasL and Fas expressions appear to have a therapeutic implication for high-grade tumors rather than a prognostic one.**

Fas ligand (FasL, CD95L) is a type II transmembrane protein of the tumor necrosis factor family that induces cells to send an apoptotic signal to cells expressing Fas (CD95, APO-1).[1,2] FasL is expressed on a limited number of cell types, including activated T cells, Sertoli cells in the testis, and epithelial cells in the anterior chamber of the eye, providing an immune privilege.[3,4] The immune privilege has been attributed to local expression of FasL, which presumably acts by inducing apoptosis of invading, Fas-bearing activated T cells.[5,6] More recently, it has been suggested that FasL expression on a subset of tumors may contribute to evasion of the immune surveillance. Induction or upregulation of functional FasL expression has been reported in several human cancers, including hepatocellular carcinoma, melanomas, lung carcinomas, glio-blastomas, a colon carcinoma cell line, liver metastases of colon adenocarcinomas, and esophageal squamous cell carcinomas.[7–14]

Fas is a type I transmembrane protein in the tumor necrosis factor receptor/nerve growth factor family and is expressed on a variety of cell types, including hepatocytes, activated B and T cells, and neutrophils.[1–3] It is also constitutively expressed on variable epithelial cells, including renal tubular cells and urothelial epithelium.[15,16] In tumors, Fas expression is heterogenous, ranging from downregulation or loss to abnormal neoexpression.[15] It is clear that cancers have a dysregulated expression of Fas and FasL system, conferring a survival advantage. Therefore, it is very important to understand FasL and Fas expression in tumors, because the growth of cancer may be controlled by Fas-mediated apoptosis.

Previous investigations have demonstrated that in renal cell carcinomas, Fas-mediated cell death pathway is functional and suggested to be one of the possible targets for a novel approach to human renal cell carcinomas.[17–20] However, these studies did not consider the prognostic factors, including histologic types. Furthermore, FasL expression in renal cell carcinomas has not been studied. Therefore, in this study, we investigated 51 cases of renal cell carcinomas and the adjacent normal renal tissues for the expression of FasL and Fas by immunohistochemical analysis. Their expressions were compared with tumor size, nuclear grade, stage, and histologic types.

MATERIALS AND METHODS Return to TOC

We studied a total of 51 cases of renal cell carcinomas and the adjacent nonneoplastic renal tissues.

The normal renal tissues were obtained from the corresponding carcinomas. The specimens were selected at the Department of Pathology in Korea University Hospitals between February 1991 and December 1998. All specimens were fixed in 10% buffered formalin, embedded in paraffin, and stained with hematoxylin-eosin and Hale colloidal iron. The renal cell carcinomas were classified into clear cell, papillary, and chromophobe subtypes, based on the Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC) workshop on renal cell carcinoma.[21] The histologic subtypes were determined by consensus among 3 pathologists after independent reviews. Nuclear grading was determined according to the criteria proposed by Fuhrman et al.[22] Stage was determined according to UICC TNM classification.[23]

Immunohistochemical studies for FasL and Fas were performed on formalin-fixed, paraffin-embedded tissues using the avidin-biotin-peroxidase complex method. Specimens were fixed in 10% neutral buffered formalin, dehydrated in graded ethanols, and embedded in paraffin. Sections were cut at 4-μm thickness, placed on poly-L-lysine coated glass slides, and air-dried overnight at room temperature. Deparaffinized and rehydrated sections were placed within boiling 1 mM EDTA solution at pH 8.0 and kept in a pressure cooker for 3 minutes to retrieve their epitopes. After blocking in methanolic peroxide, the sections were treated with stepwise additions of biotinylated antimouse antibody and streptoavidin-biotin-labeled complex and finally developed with diaminobenzidine. Primary antibodies against FasL (Transduction Laboratories, Lexington, Ky) and Fas (Transduction Laboratories) were used at a dilution of 1:200. The sections were lightly counterstained with hematoxylin. Negative controls were prepared by omission of the primary monoclonal antibodies. Formalin-fixed, paraffin-embedded sections of human tonsils showing reactive lymphoid hyperplasia were used as positive controls for FasL, and sections of human liver tissue with chronic active hepatitis served as positive controls for Fas. Immunohistochemical staining was carried out with positive and negative controls under the same condition. The relative staining intensities of normal tubular cells were graded as follows: ++, strong positive; +, positive; and −, negative. FasL or Fas expressions in carcinoma cells were graded as follows: −, no expression; ±, less than 10 positive cells; +, less than 10% positive cells; ++, less than 10% to 50% positive cells; and +++, more than 50% positive cells. High expression of FasL or Fas protein was defined when the immunostaining intensity of carcinoma cells was similar to or more intense than the adjacent tubular cells and the positive cells comprised more than 50%. When more than 50% of the cancer cells expressed FasL or Fas but the staining intensity was less intense than the adjacent tubular cells, it was considered as low expression.

The relationship between FasL and Fas expression was analyzed with the McNemar X^2 test. The expressions of FasL and Fas among groups were compared using the Fisher exact test and X^2 test. Tumor size was treated as a numerical variable and compared with the Kruskal-Wallis 1-way analysis of variance by ranks. A P value of less than .05 was considered significant.

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Clinicopathologic Findings of Renal Cell Carcinomas

Patients with renal cell carcinoma had a mean age of 51.4 years (range, 20–79 years) and showed a male-to-female ratio of 2.2:1 (35 male and 16 female). The tumor size ranged from 1.2 to 23 cm (mean, 7.5 cm). The clinicopathologic data such as histologic type, nuclear grade, and TNM stage are summarized in Table 1 .

FasL and Fas expression in Normal Renal Tissue and Urothelium

Immunohistochemically, FasL was constitutively expressed in all the nephron segments of the normal kidney, but Fas was expressed in all tubules, except for glomeruli (Table 2 and Figure 1). The proximal and distal tubules expressed both FasL and Fas more intensely than the collecting ducts or thin limbs of the Henle loop. FasL was found in the parietal layers of the Bowman capsule as well as in the glomeruli (Figure 1, left), whereas Fas was expressed only in the parietal layers of the Bowman capsule (Figure 1, A, right). The staining intensities of FasL in the glomeruli were similar to those of the thin limb of the Henle loop, but the immunoreactions were quite focal and weak compared with the proximal and distal tubules (Figure 1, A, left). In collecting ducts, which were easily recognized within the inner medulla, a distinct heterogenous expression of both FasL and Fas was found (Figure 1, C), whereas their expression was homogenous in the proximal and distal tubules (Figure 1, B). In addition, both FasL and Fas were expressed in all urothelial cells, including umbrella cells.

FasL and Fas Expression in Renal Cell Carcinomas

FasL protein was detected in all but 1 case (98.0%) of the 51 renal cell carcinomas, which was a papillary type, nuclear grade 4 and stage 3 (Table 1). FasL expression was clearly observed on the cell membrane and within the cytoplasm of almost all tumor cells (Figure 2). In 48 (94.1%) of 51 renal cell carcinomas, the staining intensity of FasL was either similar to or higher than that in the normal segments of kidney. Only 2 clear cell types and 1 papillary type expressed FasL in 10% to 50% of tumor cells and less than 10 tumor cells, respectively. The remaining expressed strongly FasL in almost all tumor cells. FasL was expressed less intensely with increasing grade ($P = .03$) and stage ($P = .006$) of renal cell carcinomas. Fuhrman grade 2 and 3 tumors expressed FasL at a much higher rate than grade 4 tumors ($P = .03$) did. However, the level of FasL expression did not statistically correlate with tumor size ($P = .40$) and histologic type ($P = .36$).

Fas protein was expressed in 38 (74.5%) of 51 renal cell carcinomas. Fas expression was seen clearly on the cell membrane and within the cytoplasm of the tumor cells like FasL (Figure 2). In fact, the staining intensity of Fas was less intense than that in the adjacent normal segments in all cases. Complete loss of Fas or minimal expression (in fewer than 10 tumor cells) was seen in 13 (25.5%) of 51 renal cell carcinomas. Grade 4 tumors expressed Fas at much higher rates than grade 2 and 3 tumors ($P = .009$). However, the level of Fas expression did not correlate with tumor size ($P = .11$), histologic type ($P = .14$), and stage ($P = .71$) (Table 1).

Both high expression of FasL and low expression of Fas protein was seen in 36 (70.6%) ($P = .04$) of 51 cases (Figure 2 and Table 3). This pattern of expression correlated well with the Fuhrman grade. Grade 2 or 3 tumors showed this expression pattern of FasL and Fas proteins, whereas grade 4 displayed overexpression of both FasL and Fas ($P < .001$). However, the expression pattern, high expression of FasL and low expression of Fas, did not statistically correlate with tumor size ($P = .31$), histologic type ($P = .07$), and stage ($P = .71$).

COMMENT Return to TOC

In this study, we found that both FasL and Fas are constitutively expressed in normal renal tubular cells and that FasL expression is enhanced in most renal cell carcinomas, whereas Fas is expressed at a lower rate in more than two thirds (76.5%) of renal cell carcinomas. In fact, the intensity of Fas expression in renal cell carcinomas was weaker than in that of normal tubular cells.

Tubular epithelial cells of normal adult kidney showed strong expression of both FasL and Fas. FasL was expressed in the glomeruli, parietal cells of the Bowman capsule, proximal and distal tubules, and

collecting ducts, as well as in the thin limbs of the Henle loop, whereas Fas was also expressed in the same areas, except for the glomeruli. The proximal and distal tubular cells expressed both FasL and Fas more intensely than other segments of the tubules. These findings are rather different from data by Leithäuser et al,[15] who showed that Fas was detected immunohistochemically only in the proximal tubules, collecting ducts, and the intermediate and basal cells of urothelium. This discrepancy between the results may be due to differences in the immunostaining methods and interpretation. In our study, we performed immunohistochemical staining by the heat-induced epitope retrieval with EDTA solution in a pressure cooker, which is one of the effective retrieval methods.[24] For the localization of specific segments of the nephrons at various levels, we observed carefully the cortex for proximal tubules, the outer medulla for distal tubules, and the inner medulla for collecting ducts and thin limbs of the Henle loop, respectively.[25] It is suggested that the constitutive FasL and Fas coexpression on adult renal tissues might play an important role for tissue homeostasis during physiologic cell turnover via an autocrine-paracrine loop.

This study clearly shows that FasL expression of renal cell carcinomas is either similar or expressed more intensely compared with that of the corresponding normal renal tissue and that FasL expression is rather decreased with increasing grade or stage. It has been known that FasL expressed in a variety of cancers is functional, resulting in apoptosis of Fas-sensitive Jurkat T leukemia cells.[9-14] Recently, Tanaka et al[26] indicated that FasL is cleaved by a putative metalloproteinase to produce a soluble form. The soluble FasL inhibited cytotoxicity of the membrane-bound FasL, indicating the membrane-bound form is the functional form. Therefore, it is thought that the FasL expressed in renal cell carcinomas may be functional, although apoptosis induction using Fas-sensitive Jurkat cells was not investigated. Overexpression of functional FasL has been reported in a wide variety of tumors and may contribute to evasion of immune surveillance by counterattacking Fas-expressing cytotoxic T cells.[7-14] However, debate continues because immune escape or privilege cannot be ascribed to a single protective mechanism such as FasL, but rather it involves an intricate orchestration of passive (low major histocompatibility complex expression, physical location) processes.[27] Taken together, it is likely that the overexpression of FasL in renal cell carcinomas may be another example of immune privilege as seen in the eye,[5] testes,[6] and some tumors.[7,8]

Fas was expressed at a lower rate or absent in more than two thirds (76.5%) of renal cell carcinomas studied, whereas normal renal tubular cells expressed Fas constitutively. In fact, when compared with the adjacent normal tissue, the intensity of Fas expression was much lower than that of normal tubules in all tumors. Low expression of Fas may be a strategy for renal cell carcinoma cells to escape immune surveillance by activated cytotoxic T cells. This hypothesis was also suggested by the studies showing that the majority of esophageal carcinomas and hepatocellular carcinomas displayed downregulation or loss of Fas.[7,14]

FasL or Fas expression did not correlate with the histologic types of renal cell carcinomas. In humans, FasL and Fas genes are located on the chromosome 1q23[28-30] and chromosome 10q24.1,[31] respectively. The loci of these chromosomes were not frequently involved by the cytogenetic abnormalites of renal cell carcinomas (clear cell type, loss of chromosome 3p, 5q, and 14q; papillary type, a combined trisomy of chromosome 7 and 17, loss of Y chromosome, trisomy of chromosomes 16, 12 and 20; chromophobe type, allelic losses at chromosome 3p, 5q and 17).[32] Thus, it is likely that tumorigenesis itself does not influence the expression of FasL or Fas in renal cell carcinomas. Since the histologic types of renal cell carcinomas reflect their putative cell of origin and variable malignant potentials, FasL or Fas expressions appear not to be a factor with a diagnostic or prognostic significance. However, nuclear grade or stage of renal cell carcinomas correlated with FasL or Fas expression. Interestingly, high-grade

carcinomas exhibited overexpression of both FasL and Fas. The coexpression of FasL and Fas could lead them to a suicidal and/or fratricidal death, as shown for activated T lymphocytes, various epithelial tissues, alcoholic hepatitis, and Hashimoto thyroiditis.[16,33–35] As such, FasL may regulate tumor growth itself via an autocrine-paracrine loop involving the Fas-FasL apoptotic pathway, and it may explain to some extent the high apoptotic index in the high-grade tumors.[36] Although the expression of FasL or Fas has no prognostic significance, it is clear that the control of FasL or Fas expression may provide a therapeutic option, especially in high-grade renal cell carcinomas.

In conclusion, this study shows that both FasL and Fas are constitutively expressed in normal adult kidney, although the intensity and pattern of expression varied according to the segments. The majority of renal cell carcinomas show both overexpression of FasL and low expression of Fas protein. However, the Fuhrman grade 4 carcinomas showed high expressions of both FasL and Fas. It is suggested that renal cancer cells may kill Fas-expressing cytotoxic T lymphocytes, leading to evade surveillance of the immune system, but may also be controlled by Fas-mediated apoptosis, especially in high-grade carcinomas.

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Table 1. Fas Ligand (FasL) and Fas Expression in Renal Cell Carcinomas*

	FasL					
	−	±	+	++	+++	−
Histologic type†						
Clear cell (n = 20)	0 (0)	0 (0)	0 (0)	2 (10)	18 (90)	2 (10)
Papillary (n = 11)	0 (0)	1 (9)	0 (0)	0 (0)	10 (91)	0 (0)
Chromophobe (n = 20)	0 (0)	0 (0)	0 (0)	0 (0)	20 (100)	3 (15)
Fuhrman grade‡						
1 (n = 0)	...	...	...	...	...	...
2 (n = 13)§	0 (0)	0 (0)	0 (0)	0 (0)	13 (100)	2 (15.4)
3 (n = 22)§	0 (0)	0 (0)	0 (0)	0 (0)	22 (100)	3 (13.6)
4 (n = 16)	0 (0)	1 (6.2)	0 (0)	2 (12.5)	13 (81.3)	0 (0)
TNM stage‖						
I (n = 26)	0 (0)	0 (0)	0 (0)	0 (0)	26 (100)	3 (11.5)
II (n = 13)	0 (0)	0 (0)	0 (0)	0 (0)	13 (100)	1 (7.7)
III (n = 12)	0 (0)	1 (8.3)	0 (0)	2 (16.7)	9 (75)	1 (8.3)
IV (n = 0)	...	...	...	...	...	...
Total (n = 51)	0 (0)	1 (2)	0 (0)	2 (3.9)	48 (94.1)	5 (9.8)

* Values represent the number (percentage) of cases and the percentage of immunoreactior than 10 positive cells; +, less than 10% positive cells; ++, less than 10% to 50% positive ce

† For Fas ligand, $P = .35$, and for Fas, $P = .14$.

‡ For Fas ligand, $P = .03$, and for Fas, $P = .01$.

§ For Fas ligand, $P = .03$, and for Fas, $P = .009$. The expression rates of grade 2 and 3 tumors

‖ For Fas ligand, $P = .006$, and for Fas, $P = .71$.

Table 2. Fas Ligand (FasL) and Fas Expression in Normal Renal Tissue and Urothelium*

	FasL (n = 51)		
	−	+	++
Glomeruli	2 (3.9)	49 (96.1)	0 (0)
Parietal cells of Bowman capsule	0 (0)	49 (96.1)	2 (3.9)
Proximal tubule	0 (0)	0 (0)	51 (100)
Thin limb of Henle loop	1 (2)	50 (98)	0 (0)
Distal tubule	0 (0)	1 (2)	50 (98)
Collecting duct	0 (0)	1 (2)	50 (98)
Urothelium			
Superficial (Umbrella) cell	0 (0)	51 (100)	0 (0)
Basal/intermediate cell	0 (0)	51 (100)	0 (0)

* Values represent the number (percentage) of cases and the intensities of immunoreactior positive; and −, negative.

Table 3. Expression Patterns of Fas Ligand (FasL) and Fas in Renal Cell Carcinomas*

	High Fas	Low Fas	Total
High FasL	12 (23.5)	36 (70.6)†	48 (94.1)
Low FasL	0 (0)	3 (5.9)	3 (5.9)
Total	**12 (23.5)**	**39 (76.5)**	**51 (100)**

* Values are number (percentage).
† $P = .04$.

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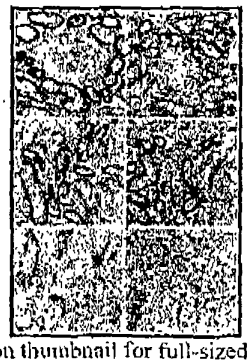

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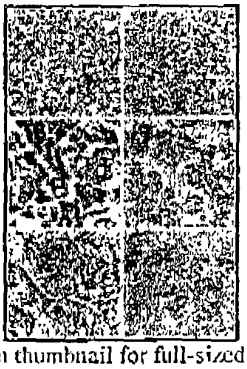
Figure 1 (p 690). Fas ligand (FasL) and Fas expression in normal renal tissue. A, FasL (left) is expressed in the glomeruli, parietal cell layers of the Bowman capsule (arrow), and proximal (P) and distal tubules of the renal cortex. The proximal and distal tubules show diffuse strong FasL expression, compared with focal, less intense immunostaining in the glomeruli. In contrast, Fas (right) is not expressed in the glomeruli. B, Both FasL (left) and Fas (right) are expressed in the distal tubules (D) and collecting ducts (C) of the outer medulla of the kidney. C, Both FasL (left) and Fas (right) are expressed in the thin limbs of the Henle loop (T) and collecting ducts (C). A distinct heterogenous pattern of expression is seen in the collecting ducts (immunoperoxidase stain, original magnification ×200).

Figure 2 (p 691). Fas ligand (FasL) and Fas expression in renal cell carcinomas. A, Clear cell type (grade 3, stage I); B, papillary type (grade 3, stage I); and C, chromophobe type (grade 3, stage II) show high expression of FasL (left) and low-expression of Fas (right) protein (immunoperoxidase stain, original magnification ×200).



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Reprints: Young-Sik Kim, MD, Department of Pathology, Korea University Ansan Hospital, College of Medicine, Korea University, 516 Gojan-Dong, Ansan City, Kyonggi Province, 425-020, Korea.